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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,038	07/10/2000	Antonio J. Grillo-Lopez	P1752R1	9334

7590 01/16/2004

Attn Wendy Lee
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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,038	GRILLO-LOPEZ ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-16,22 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-16,22 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/3/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/03/03 has been entered.

2. Claims 1, 5-16, 22 and 28 are pending.

3. Claims 1, 5-16, 22 and 28 are under examination as they read on a method of blocking an immune response to a foreign graft in a mammal, where the mammal is not suffering from a malignancy, with an antbody which binds to CD20.

4. Applicant's IDS, filed 11/5/03, is acknowledged. Examiner initial references 61, 64, 65, 70, 159-164 and 168, however no dates are indicated on the documents. In some cases the Examiner indicate the dates, however, Applicant is require to provide and confirm the dates of the above mentioned documents.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "from about 20mg/m^2 to less than 375mg/m^2" claimed in claim 13, line 2 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 11/3/03 points to the specification at page 41, lines 26-27 for support for the newly added limitation "from about 20mg/m^2 to less than 375mg/m^2" as claimed in claim 13. However, the specification does not provide a clear support such limitation. It noted that the specification on page 41, lines 26-27 discloses the range from about 20mg/m^2 to about 1000mg/m^2. The instant claim 13 now recites a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

7. Claims 1, 5-16, 22 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide sufficient enablement to block/treat any foreign graft in a mammal including GVSD or HVSD. No empirical data were provided. The specification discloses that the anti-CD20 antibodies may be used for treatment or prophylaxis of "chronic" allograft rejection or in the setting of xenotransplantation (page 47, lines 21-24). Krenger and Ferrara (immunol. Res. 15:50-73, 1996) teach that two distinct murine models immunological patterns were observed of a cute and chronic graft-versus-host disease are associated with differential activation of Type I and type 2 T cell subsets after allogeneic BMT (see page 61, 2nd col., lines 29-33). Further, Krenger and Ferrara et al teach that a classical lethal acute GVHD is linked to the preferential activation of donor T cells secreting Il-2 and IFN-g which the less severe chronic form of GVHD is characterized a type 2 cytokine response where IL-4 and IL-10 are preferentially produced after BMT (see page 61, 2nd col., lines 38-43 and page 62, lines 1-10). Thus, the specification does not provide sufficient enablement for the treat any foreign graft or GVSD or HVSD whether they are chronic or acute. Further, the kinetics of the rituximab imply that it will be less effective for the immediate problems associated with humoral rejection, but may theoretically impact later sequelae, such as chronic rejection (see Aranda et al, IDS Ref 173, Discussion).

The specification provides insufficient guidance to enable one skill in the art to use of CD20 antibodies to reducie or prevent the houst humoral and/or T cell-mediated immune responses against a graft (allogenenic or xenogenic) to an extent that a graft would be survived and maintained for a sufficient period of time to yield any beneficial use or any graft versus host reaction. There are insufficient guidance regarding depleting CD20-positive cells (granulocytes, monocytes, and T cells) using anti-CD20 Abs, which would lead to a relative enrichment of CD20-negative cells (plasma cells). Alwayn et al (Xenotransplantation, 8 :157-171, 2001) teach that antialphaGal Abs are a major barrier to clinical xenotransplantation as they are believed to initiate both hyperacute and acute humoral rejection. Alwayn et al teach that antialphaGal Abs are associated with graft destruction. Alwayn et al depletion of B cells with anti-CD20 resulted in a significant increase in antialphaGal Ab production by the plasma cells. This observation suggests that B cells are not the major source of antialphaGal Ab production. Therefore, one skilled in the art at the time the invention was made would doubt that the B-cells are associated with the graft destruction to be as a therapeutic target.

Further, at issue is whether or not the claimed method would function in "blocking an immune response to a foreign graft in a mammal" or "treat graft-versus-host or host-versus-graft dieses". The nature of the invention is such that it would require the administration of anti-CD20 antibodies such as Rituxan to prevent the allorejection response by inhibiting alloantibody production and/or affecting alloantigen presentation through depletion of antigen-presenting cells (page 47). The specification discloses that the anti-CD20 antibody may also be combined with

other induction immunosuppressive drugs such as polyclonal anti-lymphocyte antibodies or monoclonal anti-CD3 antibodies, anti-proliferative agents or combination regimens that include blockade of T cell co-stimulation, blockade of T cell adhesion molecules and blockade of T cell accessory molecules (page 47). The specification does not provide exemplification to demonstrate the ability of the anti-CD20 antibodies to block the development of xenografts or allografts.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the method of blocking an immune response to a foreign graft, GVSD or HVGD indices of administering to the animal anti-CD20 Abs can be species- and model-dependent, it is not clear that reliance on theoretical hypothesis on blocking allorejection response by inhibiting alloantibody production and/or affecting alloantigen presentation through depletion of antigen-presenting cells accurately reflects the relative human efficacy of the claimed therapeutic strategy in transplants. The specification does not adequately teach how to effectively block and treat any graft with anti-CD30 Abs or reach any therapeutic endpoint in humans by administering anti-CD20 Abs. The specification does not teach how to extrapolate data obtained from any studies to the development of effective in vivo mammalian including human therapeutic prevention and treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the anti-CD20 Abs exemplified in the specification.

However, an effective preventive/treatment protocol for the prevention/treatment of organ transplant failure resulting from graft rejection is subject to a number of factors beyond simply the administration of antibodies to the donors (GVHD). The ability of a host to suppress and thereby prevent/treat graft transplant resulting from establishing tolerance toward grafts will vary depending upon factors such as the condition of the host and the type of grafts. Further, the specification is not enabled for graft related (allografts) or graft unrelated (xenografts), which is expected to lead to more damage or/and destruction of the grafts, wherein the level of immune suppression and/or rejection is expected to be greater in xenograft recipients.

The specification does not provide sufficient teaching as to how it can be assessed that prophylaxis/treatment of GVHD or HVGD in xenograft or allograft was achieved after the administration of the therapeutic composition of the invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 11/03/03, have been fully considered, but have not been found convincing.

Applicant invites the Exnminer to consider evidence in the published literature subsequent to the filing date of the present application that shows the successful use of rituximab in blocking an immune response to a graft in a mammal not suffering from a malignancy according to the teachings of the present application. For example,

Aranda et al., Anti-CD20 Monoclonal Antibody (Rituximab) Therapy For Acute Cardiac Humoral Rejection: A Case Report" Transplantation, Vol. 73, 907-910, No. 6, 2002.

Aranda et al teach that a single case therapy for a cute cardiac humoral rejection of a 50 year old woman using Rituximab (anti-CD20 antibody). However, the claims are drawn to any graft whether it is xenograft or allograft, chronic or acute. Further, Aranda et al teach that it is not possible to assess the direct effect of rituximab on this patient's acute episode of humoral rejection because standard therapy was given in addition to anti-CD20 monoclonal antibody. Therefore, faced with results that can not be assess regarding the effect of anti-CD20 antibodies, undue experimentation would be required of the skilled artisan to determine the effect of anti-CD20 antibodies, if any, on the patient's acute episode of humoral rejection in view of the instant disclosure. It is unclear whether anti-CD20 antibodies would reduce the anti-HLA antibodies or the effect is due to the other drugs.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
January 7, 2004

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